New and Notable

A Stochastic Relationship

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Voltage-gated sodium and potassium ion channels are responsible for action potential (AP) generation and propagation in neurons. However, many other channels—voltage-gated or otherwise—participate in establishing specific patterns of firing activity, regulating AP shape, spiking frequency, and response to synaptic input. These channels are unevenly distributed across the neuronal membrane, covering with variable density the soma, the dendrites, and the axon. The voltage-gated channels in a cell are functionally coupled through the electric field created across the membrane by the separation of electrical charges between the intra- and extracellular environments. When one ion channel opens, the net flow of ions through its pore will produce a small change in membrane potential; in turn, this change in potential will be sensed by voltage-gated channels, which can further amplify, or reduce, the net ionic current, in a positive or negative feedback loop. This coupling is fundamental to the AP generation mechanism.

Voltage-gated calcium channels (Cav) are a special case: not only do they contribute to the membrane potential, but their permeant ion is a major intracellular signaling factor. In a resting cell, the intracellular Ca^{2+} ions are strongly buffered to low concentrations. However, the opening of Cav channels during an AP transiently raises the intracellular Ca^{2+} concentration well above the background. When APs repeat with high frequency, the background Ca^{2+} concentration itself can increase. Together, these fast or slow changes in intracellular Ca^{2+} levels are critical regulatory factors for the activity of many cellular functions, including transcription, and may be involved in neuronal plasticity (1). Calcium ions also directly regulate the activity of different ion channel types, most notably Ca-activated K^+ channels (2). Thus, together with the membrane potential, the intracellular Ca^{2+} concentration is another coupling factor, linking membrane potential, voltage-gated channels, Ca^{2+} ions, and calcium-sensitive channels.

A new study by Cox published in this issue of the *Biophysical Journal* (3) examines the functional relationship between Cav channels and the large-conductance, calcium-sensitive potassium channels (BK), which have been shown to form complexes in the membrane (4). For the first time, the functional complex made by a Cav channel and one or more nearby BK channels is modeled as a single unit, using stochastic algorithms.

Why is this idea so powerful? To answer, let us imagine for a moment the hydrothermal vents on the ocean floor: the ocean is dark, cold, and bare, but around each vent the water is warm, food is plenty, and life is booming (5). Likewise in the neuron: in the close proximity of an individual Cav channel that just opened, the Ca^{2+} concentration rises immediately to high levels above the background, but this short-lived Ca^{2+} gradient does not reach far and dissipates quickly. It is not surprising, then, that this ecological niche is occupied, and certain life forms can be found around the calcium vents, waiting for random servings of food. These Ca^{2+}-loving creatures are the BK channels. Clearly, the Cav-associated and the standalone BK channels will experience very different Ca^{2+} concentrations, effectively forming at least two populations with distinct gating properties.

But why not model the Cav and the BK channels separately, even when associated in a complex? Cox has shown here that when the Cav channel opens, the local Ca^{2+} concentration jumps practically instantaneously, relative to the slower BK channel kinetics. As a result, the BK channel will also instantaneously flip into a different gating mode, with conceptually the same number of conformations but quantitatively different transition rates, as they are modulated by Ca^{2+}. Thus, inasmuch as the state of the BK channel is coupled to the state of the Cav channel, the Cav/BK complex could be described by a single state-model. Incidentally, voltage-gated sodium channels present a similar problem: while the Hodgkin and Huxley formalism described activation and inactivation as separate processes, more recent studies couple them into a single state-model, recognizing the evidence that the rates of inactivation depend on the state of activation (6).

Obviously, modeling the complex as a single unit makes sense, but why run stochastic simulations? This has nothing to do with the coupling between Cav and BK channels, which can be equally well described with deterministic algorithms. The simple reason is that stochastic methods are more appropriate when considering relatively small numbers of particles, e.g., tens to thousands. Also, a very important factor to consider is the sheer magnitude of the BK single channel current, which is ~10 times greater than that of Cav channels. This is substantial relative to the input resistance of many types of cells, particularly when it occurs in small and electrotonically isolated compartments, such as the central nerve terminals. A random change in one single Cav/BK complex may be enough to switch the output state of the neuron, and this cannot be captured with deterministic simulations that represent average behavior but not fluctuations.

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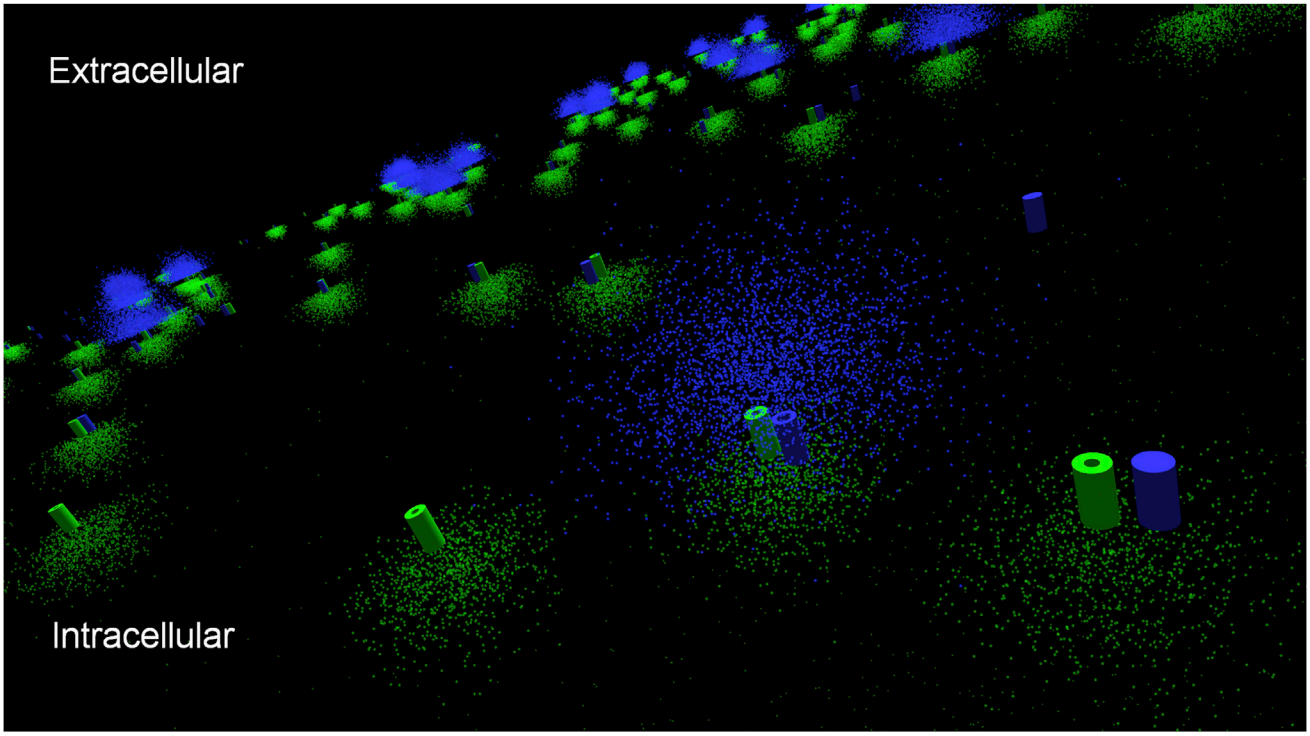

FIGURE 1 A stochastic landscape with Ca^{2+} vents and BK channels. The illustration envisions the membrane distribution and the activity of Cav and BK channels during an action potential, according to the study by Cox (3). As shown, most of the Cav (*green cylinders*) and BK (*blue*) channels are associated in 1:1 complexes, but some are standalone. Most of the Cav channels are open, but only 30% of the BK channels are open, even under the Ca^{2+} umbrella of their Cav partners. Also shown are the Ca^{2+} (*green*) and K^+ (*blue*) ions entering or exiting the cell through open Cav or BK channels, and the background intracellular Ca^{2+} ions.

The stochastic simulations done by Cox bring some interesting and surprising results. Most notably, the modeling predicts that, during a typical cortical AP, the Cav channel in a complex will be activated by voltage almost every time, but the associated BK channels will simply not open at all in two out of three occasions, statistically speaking (see Fig. 1). We further learn that this success rate of 30% is highly dependent on the duration of the AP and on the Ca^{2+} concentration, as determined by the distance between the two channels in the complex and by the activity of fast intracellular Ca^{2+} buffers. The bottom line is that the response of the BK channel in the complex is not limited by the kinetics of Cav channels: these are fast enough, and can follow even fast trains of action potentials. Instead, the BK channel is intrinsically slow relative to the timescale of an AP.

What I find very exciting is the potential number of functional studies that are enabled by the models proposed by Cox. Developed from experimental electrophysiology data, these models are reasonably accurate and are well anchored in biophysical structure-function studies, yet they are tractable enough for neuro-computational research. With these models, the contribution of BK channels to neuronal firing can be tested under a variety of paradigms: BK in complex with Cav channels or standalone, stochastic versus deterministic, compartmentalized or not, and so on. The models can also be expanded to account for the effects of auxiliary BK subunits (7).

Even more exciting is the possibility of using these models in dynamic-clamp studies, where an ion channel model can be tested in a live neuron, against a background of unknown conductances (8). The neat advantage of modeling the complex as a single unit is that the Ca^{2+} concentration becomes an implicit rather than explicit factor, which might substantially simplify the computation (9). Existing dynamic-clamp algorithms and software can handle the large state-models describing the BK/Cav complex, and can integrate them stochastically (10). In conclusion, although it is never easy to bridge the gap between molecular biophysics and cellular neuroscience, the study by Cox has done so quite successfully.

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